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A CLINICAL STUDY.

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NUCLEINS—A CLINICAL STUDY.

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INTRODUCTION.—The history of the study of nucleins extends over a period of more than sixty years, running back to the time of Braconnot (1831); but it is only within recent times that any systematic attempts have been made to determine their chemical and physiological properties with a view to their employment in the domain of practical therapeutics. The object of the present paper is to present a concise epitome of the subject, referring briefly to the more important questions likely to occur to the general practitioner relating to the source and method of preparation, physiological properties, therapeutic range, with clinical indications for their employment.

SOURCE AND PREPARATION.—*Scientifically*, nuclein is described as a phosphorized proteid, the phosphorus existing in the form of nucleinic acid, combined with a highly complex basic substance. This basic substance yields as decomposition products one or more of the so-called xanthine bodies, adenin, guanin, sarkin, and xanthin. The available sources are as follows: Yeast-cells, yolk of egg, the spleen,

the blood, the testicles, the bone marrow, the brain substance, and the thyreoid and thymus glands.

Historically, nucleins have been studied by Braconnot (1831), Quevene (1838), Schlossberger (1834), Miescher (1845), Bechamp (1865), and later by Hoppe-Seyler, Lubavin, von Jaksch, and Plösz. In 1879 Kossel demonstrated that they possessed germicidal properties, and ten years later they received attention at the hands of Altmann. Liebermann prepared an artificial nuclein from albumin and metaphosphoric acid, and here should also be mentioned the names of Geohegan, Malfatti, Horbaczewski, and finally, in 1893, Vaughan, of America, Althaus, of England, and Germain Sée, of France.*

* The appended references to contributions by the writer may be of some interest to those who wish to investigate further the clinical researches on this subject:

Nuclein Therapy. *American Therapist*, December, 1893.

The Principle involved in the Subcutaneous Use of Blood Serum. *Loc. cit.*, January, 1894.

Clinical Observations on Nuclein Solutions. *Loc. cit.*, February, 1894.

Thrashing over Old Straw. *Loc. cit.*, February, 1894.

A Note on the Employment of Nuclein Solution. *New York Medical Journal*, March 24, 1894.

The Treatment of Diarrhoeal Disease. *Transactions of the Medical Society of the State of Pennsylvania*, 1894 (*American Therapist*, May, 1894).

Organic Extracts. *American Therapist*, July, 1894.

Nuclein—What is It? *Medical Summary*, July, 1894.

A Modern Idea in Scientific Medicine. *Medical Record*, August 11, 1894.

Autumnal Catarrh. *American Therapist*, August, 1894.

Professor Vaughan has published the following papers:

The Principles of Immunity and Cure in Infectious Diseases. *American Therapist*, September, 1893 (*Transactions of the First Pan-American Congress*, Washington, D. C., 1893).

The Nature of the Germicidal Constituent of Blood Serum. *Medical*

Yeast nuclein, according to Vaughan, is prepared as follows: Brewer's yeast is extracted with dilute alkali and filtered, and the filtrate precipitated with dilute hydrochloric acid. The precipitate is redissolved in alkali and reprecipitated with acid several times, and is finally dissolved in 0.25 per cent. of potassium hydrate.

Testicular nuclein is prepared by means of artificial digestion, after a preliminary maceration and extraction with a mixture of equal volumes of absolute alcohol and ether. The testicular substance is then digested for some days with pepsin and 0.2-per-cent. hydrochloric acid, the undigested portion being collected on a filter paper and worked, first, with 0.2-per-cent. hydrochloric acid, then with alcohol. The final step consists in dissolving the precipitate in a 0.5-per cent. solution of potassium hydrate and filtering through a Chamberlain filter without pressure.

Nuclein solutions are also prepared from the blood, the spleen, the bone marrow, the brain, and the thyroid and thymus glands in the same manner as described for the preparation of testicular nuclein; but, as all these solutions obtained in this way from animal sources contain a small percentage of albumin, this fact must be taken into consideration when using the product hypodermically. There is also danger of sloughing, owing to the presence of the alkali, when large doses are administered in this manner. Through the courtesy of a competent chemist I have been

News, December 23, 1893 (read by title, First Pan-American Medical Congress, Washington, D. C., 1893).

The Nucleins and Nuclein Therapy. *Journal of the American Medical Association*, June 9, 1894 (*Transactions of the Illinois State Medical Society*, 1894).

Professor Chittenden has also published a paper bearing upon this subject (Nuclein and its Relationship to Uric Acid), *Dietetic and Hygienic Gazette*, February, 1894.

able to conduct my later experiments with solutions absolutely free from albumin or excess of alkali, which give rise to no untoward effects either hypodermically or when introduced into the system by way of the stomach. After a careful survey of the current literature, together with an extended series of clinical tests, the conclusion was reached that the thyreoid and thymus glands offered the most valuable and at the same time the most available source for obtaining this product, and, with some important modifications of Vaughan's process, a permanent and non-irritant solution of definite strength could be depended upon. Investigations are still in progress, and it is probable that a slightly modified product, a trifle less effective therapeutically, will in the end be found which can be prepared at a nominal expense.

PHYSIOLOGICAL PROPERTIES.—Naturally, in studying the physiological properties of any remedy, we must consider the effect which results from its presence in the organism—*i. e.*, when brought into contact with the tissues; but it is not sufficient for the present demands of science simply to assert that a drug "stimulates," or "acts as a "sedative," unless we are prepared to offer some rational and satisfactory explanation of the mode by which such stimulation or sedation is produced. In the case of nuclein, for example, it is now well known that this is the name applied to a product more or less constantly manufactured by certain leucocytes (the multinuclear white blood-corpuscles), and, being distributed throughout the tissues by means of the lymph and blood vascular systems, a normal functional activity is maintained in the protoplasm. Now, poisonous substances produce stimulation of the protoplasm through the irritation set up, and, if long continued, this irritability is exhausted, when sedation follows; but it seems that Nature's laboratory is adapted to the production of a

protoplasmic stimulant, possessing all the properties of an antiseptic which is non-irritant, and when, through faulty metabolism, leucocytosis is defective, nuclein can be artificially supplied.

It will not be out of place here to consider the methods of Nature in resisting the inroads or progress of disease, or the aim of physiological medication in the attempt to produce artificial immunity. Taking diphtheria as an illustration, the question may be asked, Why does not the disease persist so long as life continues? The answer to this will be, that the conservative processes of the human economy are sufficient, along with suitable medication, to arrest its progress; but this explanation, from a scientific standpoint, is utterly worthless, although it has done duty and has been repeated indefinitely for generations. How shall we explain the effects of physiological antagonism by inoculation with solutions prepared from pure cultures of the pathogenic micro-organism? In this category would also fall the method of preventing cholera, pneumonia, hydrophobia, tetanus, and the arrest and cure of certain forms of cancerous affections by means of pure cultures of the bacteria associated with the respective disorders. The following outline would seem to be a more appropriate and withal a scientific elucidation of this most perplexing problem: The vitality of the animal organism depends upon the integrity and normal functional activity of the cells. Derangement of the various organs is always the result of functional or organic perturbation of the cell life or cell activity, and upon this well-known fact rests the modern doctrine of cellular therapy. All, or nearly all, remedial agents are exhibited with a view to modify, to increase, or diminish cellular activity, so that cellular therapy is but a new name used to designate a method which has universally prevailed since the dawn of medical history. The scientific

search-light has but revealed its existence, while the bacterial torch enables us to fix its position.

Now, these cells, which make up the different organs and structures, are themselves composed of cells—protoplasmic cells—and it is necessary, therefore, in order to modify their functional activity, that the protoplasm should be influenced, this being effected through the medium of the blood and intercellular fluids. Thus, the protoplasm is constantly bathed in fluids containing nutritive pabulum (and oxygen), which is taken up, and it gives off in return carbonic acid and other waste products. The protoplasm likewise possesses the power to convert oxygen into ozone, which is also a powerful antiseptic and deodorant.

Continuing this line of inquiry, we find that the power to resist or withstand disease is now attributed to “defensive proteids,” and recent investigations clearly point to nuclein as one of the most effective proteids, if not the principal one, embraced in this modern physiological complex. Physiological investigation shows that nuclein possesses distinct antiseptic properties, and clinical observation has repeatedly demonstrated its therapeutic virtues in a long list of hitherto vexatious and intractable diseases. These results, according to my interpretation of physiological processes, are due to the influence of nuclein upon the protoplasmic cells; hence the term cellular therapy, nuclein therapy being an important subdivision.

During the progress of disease, more especially disease characterized by active inflammation, when nutrition is fairly maintained, the polynuclear white blood corpuscles rapidly increase in number (inflammatory leucocytosis), and it is believed that at this stage they manufacture or produce nuclein in much larger quantity than under normal requirements. The nuclein in solution is thus brought into direct contact with the protoplasmic cells, and as a

consequence their ability to resist disease, or rather, we should say, bacteria and their products, is measurably increased, not to mention the influence which is exerted directly by the presence in the blood and intercellular fluids of such a powerful antiseptic.

We have here, then, a lucid and at the same time rational explanation of the *vis medicatrix naturæ*, as demonstrated by physiological experimentation and confirmed by clinical observation. Health is maintained and resistance to disease effected mainly through the influence of nuclein as the most active of the so-called "defensive proteids."

It is now a well-recognized fact in physiology that in confirmed drunkards the effect of alcohol on the protoplasmic cells can be demonstrated—alcoholized protoplasm—and experiments now under way give promise that we shall be able shortly to estimate in like manner the effect of long-continued opium addiction—morphinized protoplasm—all going to show that the protoplasm may be subjected to what might be termed an educational process. Such a process, we are warranted in assuming, takes place during the progress of disease, the protoplasmic cells in time becoming immune against infection.

The foregoing appears to cover the main points involved when replying to the question relating to the persistence of disease, while it affords a scientific explanation of the conservative processes of Nature, although there are still remaining many important details which can be filled in by the intelligent and thoughtful physician.

THERAPEUTIC RANGE.—The therapeutic range of nuclein will manifestly be determined by studying its proper physiological rôle in the economy, bearing in mind that it possesses a twofold action—upon the blood and upon the nervous system. Wherever Nature provides for the elimination of poisons or waste products of any description,

there shall we find nuclein. Were it not for the antiseptic properties of nuclein, as it is poured into the stomach and intestine in combination with the normal secretions, what would be the condition of the alimentary tract at the end of twenty-four hours? Had not a wise provision been made for the protection of the mucous membrane of the pulmonary structures and upper air-passages, how long would it be until decomposition would supplant normal elimination? And the same train of thought applies with equal force to the skin, the kidneys, and the entire glandular system. The condition of affairs may be compared with an island, or even a large country, traversed by a complete system of railroads and provided with telegraph lines—diverging, intersecting, connecting—with public and private roads extending in every direction, all under one central management. In the case of war, famine, or pestilence, which may be likened to disease, the whole commercial mechanism of the country is manipulated with the sole object of relieving the local distress, and, like the little blood-corpuscles in disease, every inhabitant exerts his individual effort to the best of his ability in the hope of being able to contribute something toward restoring normal conditions.

We have in the recent strikes a modern instance of physiological concentration in the arrest of disease, as contrasted with the ancient *régime* which advocated counter-irritation. Had the authorities at the time of the Chicago riots undertaken to quell the disturbance by a show of fighting a thousand miles away, anarchy might still be present with us; but by distributing soldiers and concentrating a police force at the points of rebellion, the vicious element was subdued and order re-established. Just so it is in disease; Nature contrives to afford protection by means of the defensive proteids. We have an appropriate

illustration of this in the case of boils, carbuncles, and abscesses. The same holds good also in the case of intestinal troubles—diarrhœa, dysentery, peritonitis, and typhoid fever; and the principle extends to pulmonary and bronchial affections, shown by the increased secretion, where Nature attempts to correct defects by additional work.

Taking a comprehensive survey of the subject in hand, we should assume that the exhibition of nuclein would be useful, first, in the treatment of all forms of anæmia, where nutrition is below par and digestion so impaired that insufficient pabulum is supplied to the white blood-corpuscles. By enriching the blood through the artificial supply of nuclein, the normal functions of elimination are improved and leucocytosis restored. Malaria, especially of the chronic or recurrent type, is promptly and favorably modified by the exhibition of nuclein. In both diseases the effect of medication can be demonstrated from time to time by an examination of the blood. In digestive disorders, whether occurring alone, associated with or dependent upon other disease, whether affecting the stomach or intestinal tract, nuclein solutions are most efficacious. Pulmonary disease, tuberculosis, pleurisy, pneumonia, and pleuro-pneumonia and bronchial affections generally respond promptly to nuclein medication; but a caution should be added to the effect that too much must not be expected of nucleins, presently to be more fully elaborated. In diseases of the skin arising from imperfect elimination or suboxidation, the administration of nuclein is attended with the most gratifying results; and it is even serviceable in correcting cutaneous lesions due to specific infection, doubtless owing to the improved character of the insensible transpiration. Derangements of the renal functions are perceptibly improved by nuclein. In a marked case of albuminuria, the urine was

increased, the percentage of albumin lessened, œdema of the extremities and abdominal distention diminished, and there occurred a decided improvement in the digestive function. The effect of nuclein upon the kidneys during the progress of disease elsewhere is not especially marked, the urinary flow being slightly increased, but the general character of the water is distinctly improved.

From the preceding remarks, the effect of nuclein upon the nervous system will be inferred. When disordered innervation results from faulty assimilation or defective elimination, its beneficial influence becomes quickly apparent, but its virtues are particularly noticeable when the history of the disease enables us to designate some local ailment or derangement as the exciting cause for the persistence of the malady. Thus, in females, menstrual irregularities may be responsible for a mild form of melancholia, which promptly subsides upon re-establishment of a more active tissue metabolism. In men, immoderate coffee-drinking not infrequently paves the way for subsequent cerebral disturbances. Upon removal of the cause the hepatic functions regain their vitality, and with the addition of nuclein elimination at distant points is favored.

The stimulant effect upon the cerebral functions can easily be demonstrated; taken at a time when the vital powers are depressed and the physical system exhausted from overwork, a few doses, often a single dose, creates a feeling of mental buoyancy; the step becomes firm and elastic and ambition supplants languor. This property has frequently attracted attention in the aged and in those suffering from chronic maladies.

The foregoing recapitulation embraces substantially the groundwork of nuclein therapy from the standpoint of the clinician; but in order to give the present article a practical turn it will be advisable to enter somewhat into detail re-

specting several of the more prevalent maladies common to this latitude.

CLINICAL INDICATIONS.—*Anæmia*.—Anæmia is essentially a wasting disease, the nutrition of the blood being impaired by the presence of waste products and other poisonous elements remaining in the system. Persons thus affected suffer from headache, neuralgia, various forms of catarrh, fugitive rheumatic pains, lack of appetite, sleeplessness, and constipation. The facial expression is indicative of weariness, the gait is slow and unsteady instead of being elastic and firm, while mental hebetude is often most pronounced. This condition is liable to appear in both young and old in every station of life, but it is more particularly noticeable in young girls and those who have had malaria or some lingering disease. It is frequently marked as the sequela of acute diseases, convalescence being tardy owing to faulty assimilation.

An examination of the blood shows that the red corpuscles are in an unhealthy condition, and, as a consequence, are unable to carry oxygen to the tissues; hence, combustion is lessened, the vitality of the system reduced, and the patient becomes susceptible to other diseases—pleurisy, pneumonia, pleuro-pneumonia, bronchitis, and rheumatism in winter, and the usual bowel troubles, typhoid fever, subacute and chronic catarrh in summer and autumn. To remove these irritants and restore the function of the little red blood-globules, of which there are about two hundred trillions in the human body, is a work of no small magnitude, and heretofore has required much time, patience, and skill on the part of the physician; but with the exhibition of nuclein, suitable diet, and proper hygiene, a favorable impression is produced at once, and the patient gains perceptibly from day to day. Nuclein, however, is not strictly curative without these adjuvants,

but it paves the way, setting the patient on his feet as it were, and does not preclude the use of other approved medicaments. An examination of the blood under the microscope discovers the true condition, and enables the physician to determine progress from time to time.

Malarial Disease.—This disease is better understood than in former years, since it has now been repeatedly demonstrated that a vegetable micro-organism is present in the blood. Under the microscope the influence of this parasite upon the red blood-corpuscles can be studied, and with its disappearance the disease subsides. The presence of nuclein in the blood and intercellular fluids appears to have a demoralizing effect upon the micro-organism and stimulates the blood and tissues to discharge an unwelcome guest, a few days only being required to produce a favorable change in the condition of the patient. The suggestion is thrown out here that possibly this effect is due more to the stimulation of the leucocytes (leucocytosis) than to the direct action of the substance upon either the blood or the parasite; but at any rate the transformation is effected without the least disagreeable symptom or untoward effect such as characterizes the treatment by quinine. Chronic cases, and those which show a disposition to return spring and autumn (recurrent malarial disease), are readily controlled by nuclein, improvement being observed within a few days; the languid feeling disappears, appetite returns, the bowels become regular, pain over the liver and in the back vanishes, the muddy, sallow, and greasy appearance of the skin clears up, and physical and mental activity no longer seem burdensome. Rarely will it be necessary to exhibit other medicines for the relief of this troublesome affection, except for the purpose of supplying the system with certain elementary substances that it has failed to secure because of long-continued malassimilation.

Bronchial Affections.—In the case of bronchial affections, subacute and chronic, nuclein shows its sterling value as a remedial agent. The health of most persons thus affected is a trifle below par, and as a consequence the mucous membrane lining the tubes is called upon to perform vicariously the function of elimination. Hitherto, treatment has consisted in the exhibition of remedies calculated to *increase* secretion, while the wise physician should aim to *lessen* secretion, endeavoring at the same time to increase the activity of elimination at other points, thus reducing the output through the bronchial tubes, and this purpose nuclein most satisfactorily accomplishes. It regularly and persistently augments the functional activity of the skin, the kidneys, the liver, and produces a favorable action upon the bowels, probably through increased cellular activity, both systemic and locally at the points of elimination. As a result, cough subsides, expectoration ceases, the appetite improves, and the patient gains strength, because, through this increased cellular activity, the normal functions are restored by a process which is in harmony with Nature's methods and in conformity with her laws.

Humid asthma and nearly all forms of *autumnal catarrh* are amenable to treatment by nuclein solutions; but in many of these cases, owing to the debilitated condition of the muscular system, it will be advisable to combine with its administration the use of strychnine in some form, preferably small doses of the arsenite.

Influenza.—My experience with nuclein solutions in combating influenzal complications during the past two winters has been remarkably favorable—so much so that in mild cases no other remedy has been employed, except for the control of special symptoms, such as accelerated pulse, headache, and other neuralgic pains. In convalescence from this disease, with the addition of small doses of

strychnine arsenite (one one-hundredth of a grain every two hours), recovery is remarkably prompt and apparently complete; cough and expectoration subside, strength is regained, appetite restored, and the patient is up and about within a few days after the acute stage has passed. There is no pronounced weakness, no lingering debility, and no demand for continued medication.

Pulmonary Diseases.—In the treatment of pneumonia, pleuro-pneumonia, pleurisy, and tuberculosis, the beneficial action of this remedy is sufficiently marked to be worthy of mention, although it is not advocated as a curative agent. In pneumonia, for example, when the circulation is under control, in the absence of hyperthermia, when elimination by the natural channels is arrested—shown by the embarrassed respiration and cardiac debility—solutions of nuclein can be depended upon to rekindle the dying flame by contributing toward the restoration of the normal condition of the blood. Still, there must be some doubt as to whether nuclein actually supplies something that is wanting in these cases; rather it stimulates leucocytosis, thus augmenting the antiseptic properties of this fluid. The same is true of its action in the treatment of pleurisy.

In tuberculosis it lessens the cough by diminishing expectoration, improves the appetite, regulates the bowels, increases elimination by the skin and kidneys, decreases the frequency of the exacerbations due to extension of the disease, controls in a measure the *night sweats*, and creates a feeling of well-being, while it does not interfere with the administration of other medicaments hitherto so highly prized for their antiseptic properties.

Disorders of Digestion.—In all functional disorders of the digestive system, diet being regulated, the effects are apparent within a few days. It also possesses a high degree of utility in acute attacks, more especially after the

initial stage. Nuclein is almost a specific in the treatment of tonsillitis (amygdalitis), follicular and parenchymatous, arising from digestive disturbances superinduced by cold and exposure. Indeed, in every variety of throat trouble its virtues are manifested within a few hours, although relief is less marked in those cases associated with a rheumatic diathesis.

Leucocytosis being defective in typhoid fever, the advantages of nuclein in this disease will at once suggest themselves, and as an adjuvant to modern antiseptic methods—for its influence upon nutrition—it will eventually occupy a position of no mean significance.

Diphtheria.—In quite a large number of cases where all the symptoms pointed to diphtheria as the true condition I have found nuclein solutions most efficacious, the false membrane, angina, anorexia, and restlessness all disappearing in less than twenty-four hours; and, although some fever remains for a day or two, if seen early in the attack, the most forbidding symptoms promptly yield to this form of medication. Being absolutely tasteless, prompt in its action, and entirely free from objectionable after-effects, children take it readily, frequently asking the nurse if it is “time for the medicine.”

ADMINISTRATION.—The administration of nuclein solutions differs in no wise from that of other remedies. The usual dose for an adult is, approximately, one third of a minim of the standard solution adopted, and for convenience and economy it is put in the form of tablets or granules. This dose can be repeated at intervals of from two to four hours; but in acute cases, where the patient is seen late in the day, the dose may be repeated at intervals of an hour for that day. For a child five years of age the dose should be about one third of this quantity, which can be regulated by solution in water.

In the treatment of throat troubles some advantage appears to be gained by allowing the tablet or granule to dissolve in the mouth. Tablets have been prepared for me by Mr. Charles Leedom, a local druggist of this city.

Hypodermically, notably in the case of malaria and anæmia, I have administered much larger doses, usually beginning with five drops and increasing the dose at each visit on alternate days until eight, ten, or twelve drops were given in this manner. In one case of long-continued malaria I exhibited the equivalent of a drachm, not only without untoward effect, but with decided benefit.

There are practically no contraindications, except perhaps perfect health, since, so far as my observations extend, this solution is non-toxic. The only perceptible symptoms which might be regarded as at all unfavorable, and these are inconstant, are slight passive congestion of the pharyngeal structures occasionally, increased flow of urine, and generally the development of sulphureted-hydrogen gas in the intestine; but these defects may be avoided by decreasing the dose.

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